



The Biologics License Application Process

An Overview

What is a Biologics License Application (BLA)?

A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

21 CFR 601.2

CDER Regulatory Authority

● BIOLOGICS

- Investigational New Drug Exemptions (IND, 21 CFR 312)
- Biologics License Applications (BLA, 21 CFR 600-680)

● EXAMPLES

- Vaccines and allergenic products
- Blood Products (including blood grouping reagents and donor screening tests for bloodborne pathogens)
- Cellular & gene therapies, xenotransplantation)

Who Submits a BLA ?

MANUFACTURER (Applicant)

- Any legal person or entity who is engaged in manufacture

or

- An applicant for a license who takes responsibility for compliance with product and establishment standards

What is in a BLA?

- **Form FDA 356h (cover sheet)**
- **Applicant Information**
- **Product / Manufacturing information**
- **Pre-clinical studies**
- **Clinical studies**
- **Labeling**

BLA – Applicant Information

- **Name, address & phone number**
- **Name & address of facilities**
- **Authorized official**

BLA – Product/Manufacturing Information

- **Source material / raw materials**
- **Manufacturing process and controls**
- **Formulation**
- **Facility information**
- **Contamination/cross-contamination information**
- **Environmental assessment or categorical exclusion**

BLA – Safety, Efficacy and Use Information

- **Pre-clinical studies**
- **Clinical studies**
- **Labeling**

International Harmonization

Using the CTD (Common Technical Document)

- An agreed upon common format for the modular presentation of summaries, reports and data
- Content is harmonized to the extent of relevant ICH guidelines
- Guidance for Industry:
Submitting Marketing Applications According to the ICH-CTD Format - General Considerations
 - <http://www.fda.gov/cber/gdlns/mrktapich.pdf>

Electronic Submissions

- **Submission of BLA/S may be made on paper or electronically**
- **Submissions should be made in accordance with published guidance:**
 - <http://www.fda.gov/cber/esub/esub.htm>

Before the BLA is Submitted

- **Pre-BLA meeting**
 - **CDER SOPP 8101.1 Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants**
- **Identify potential review committee**
- **Consider Advisory Committee needs & schedule**
- **Arrange for BiMo Inspection**

The Review Committee

**CONSTITUTED TO CONTAIN THE
NECESSARY EXPERTISE TO
REVIEW THE SUBMISSION**

Responsibilities – Chairperson/Lead

- **CONSTITUTE** the committee
- **ASSIGN** sections for review
- **SCHEDULE** and **CONDUCT** meetings
- **WRITE** “action” letters
- **PRESENT** at Advisory Committee Meetings
- **REQUEST** a pre-license inspection
- **PREPARE** a Summary of Basis for Approval (SBA)

Responsibilities Regulatory Project Manager

MANAGE the review of the application
REVIEW assigned portions of application
PERFORM quality control check on the review
ASSURE reviews are documented properly
ASSURE review of labeling is complete
COORDINATE compliance status check
PREPARE approval letter for new products
PREPARE finding of no significant impact

Responsibilities Discipline Reviewer

- **REVIEW** assigned sections of the application
- **WRITE** an annotated review memo
- **ATTEND** review committee meetings
- **COMMUNICATE** with the applicant as necessary and document the discussion (as per Staff Manual Guide 2126.2)
- **PREPARE** for Advisory Committee meetings
- **PARTICIPATE** in the pre-approval inspection (if necessary)
- **CONSIDER** if a public health and/or research questions need to be answered relative to product approval

Application Received

- **Administrative processing**
 - Submission tracking number assigned (STN)
 - data entry
 - user fee verification
- **First committee meeting**
 - review assignments
 - time frames

SUBMISSION TRACKING NUMBER
aaaaaa.bbbb/cccc



Filing Review

- **Review for completeness**
 - RTF policy
 - CBER SOPP 8404 Refusal to File Guidance for Product License Applications and Establishment License Applications
- **Filing meeting**
- **Filing letter**
- **Communicate any significant deficiencies noted up to that time (but not a complete review)**

Refuse To File

- A refusal to file (RTF) letter is issued when the submission has been deemed not sufficiently complete for a meaningful review
- 21 CFR601.2(a), RTF Policy, SOPP 8404
 - The Applicant may request that the submission be Filed Over Protest: SOPP 8404.1

Complete Review

- **Substantive review**
 - Information requests
 - Review memos
 - Discipline reviews
 - labeling
 - lot release protocols
- **Inspections**
 - Facility
 - Bioresearch Monitoring
- **Advisory Committee presentation**

Information Requests (IRs)

- Issued while the review is in progress
- Requests information needed to continue the review
- IRs may be made by letter, telephone or FAX
- IRs are documented in the file
- The response to an information request should not be so great as to constitute a major amendment
- Responses to information requests do not necessarily have to be reviewed in the current review cycle
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1

Discipline Reviews (DRs)

- A DR letter is issued when a particular discipline (clinical, CMC, etc.) has finished its review, but the complete review is not yet done
- A DR letter contains comments and questions that might appear in the action letter
- Responses to DR letters need not necessarily be reviewed prior to issuance of the action letter
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1

Administrative Record

- Paper trail documenting the decision making process and basis for the decision
- Copies of Telecons, FAXes, Review Memos, Meeting Minutes, etc., become part of the administrative record and are entered into the file and the tracking system

Action Decision

- **After a complete review is finished**
 - Inspections
 - Advisory Committee
- **Review Committee meeting**
 - Outstanding issues
 - Agreements & commitments
- **License action recommendation**
 - Not ready for approval
 - Approval

ACTION

Not Ready for Approval

- **COMPLETE RESPONSE LETTER**

- Itemizes all deficiencies in the application that must be corrected prior to approval
- Stops the review clock

- **RESUBMISSION**

- Class 1 or 2
- Restarts the clock

PDUFA Resubmissions

- **Guidance for Industry: Classifying Resubmissions in Response to Action Letters, May 14, 1998**
- **SOPP 8405.1 Procedures for the Classification of Resubmissions of an Application for a Product Covered by PDUFA III**

Performance Goals (con't)

Resubmitted Applications

- **Class 1**
 - 90% in 2 months
- **Class 2**
 - 90% in 6 months
- **Clinical Hold Responses**
 - 90% in 30 days
- **Major Dispute Resolution**
 - 90% in 30 days
- **Protocol Assessments**
 - 90% in 45 days

Dispute Resolution

- **Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level**
- **SOPP 8005 Major Dispute Resolution Process (2/11/99)**

ACTION

Approval

- **Compliance check**
- **Summary of Basis for Approval (SBA)**
- **Finding of No Significant Impact (FONSI) or confirm categorical exclusion**
- **Approval letter**
 - **Grants permission to distribute**
 - **Itemizes all agreements & commitments**
- **Issue license**

Rules of the Road for Reviewers

- **SGRA**
 - **SOPPs**
 - **Guidances**
 - **Regulations**
 - **Acts**